REMARKS

Claims 1-21 are pending in the application. Claims 1-5 and 10-12 are withdrawn from consideration as being drawn to a non-elected invention.

No new matter has been added. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 6-9 and 13-21 Under 35 U.S.C. § 112, First Paragraph

Claims 6-9 and 13-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that the specification does not provide adequate written description for the claimed invention because, while the specification discloses the full length sequence of murine DEC-205 protein, it only discloses a partial sequence for human DEC-205. The Examiner asserts that, because human DEC-205 is approximately 1800 amino acids in length, the recitation in the claim of a 30 or 25 amino acid sequence derived from human DEC-205 does not provide adequate written description of a molecule that is almost 1800 amino acids in length. The Examiner further asserts that the claims encompass antibodies that bind any immunogenic epitope on the approximately 1775 undisclosed amino acids of DEC 205, and that the term human DEC-205 presumably encompasses full length human DEC-205, as well as undescribed mutants and alleles of human DEC-205.

Applicants respectfully traverse this rejection for at least the following reasons.

Claims 13-17 and 18-21

Specifically, contrary to the Examiner's opinion that the claimed antibody conjugates "bind any immunogenic epitope on the approximately 1775 undisclosed amino acids of DEC 205," claims 13-17 are drawn to antibody conjugates which do, indeed, bind to a particular epitope of human DEC-205, namely the C-terminal sequence (SEQ ID NO: 7).

Similarly, that the present specification teaches a partial human DEC-205 sequence is also irrelevant with respect to claims 18-21, since these claims are drawn to methods employing antibody conjugates that bind to *full length murine DEC-205 protein* (SEQ ID NO: 10). Thus, the Examiner's statement that the antibody conjugates of claims 18-21 bind to "undisclosed amino acids of DEC 205" is incorrect. Indeed, the full length sequence of murine DEC 205 is explicitly provided in the present application as SEQ ID NO: 10. Moreover, while the antibody

conjugates of claims 18-21 also cross-react with human DEC-205, the epitopes of human DEC-205 that the conjugates bind to are thus, by definition, shared with (i.e., cross-reactive with) murine DEC-205. As such, the sequence of these epitopes is provided as part of the full length murine DEC-205 sequence recited in the claims (SEQ ID NO:10).

For at least the reasons above, the reasons provided by the Examiner for rejecting claims 13-17 and 18-21 as lacking written description under 35 U.S.C. §112, first paragraph, do not apply or support the rejection.

Claims 6-9

With respect to claims 6- 9, drawn to methods which employ antibody conjugates that bind to human DEC-205 protein comprising the amino acid sequence of SEQ ID NO:7, Applicants respectfully note that while Applicants' specification does not recite the full length human DEC-205 sequence, or the sequence of each and every variant of human DEC-205 (if such variants even exist), this does not *de facto* mean that the pending claims fail to comply with the written description requirement. Importantly, it is well-established that the written description standard is not a bright line test, but instead takes into consideration a number of different factors. As discussed in detail below, Applicants' disclosure of the partial human DEC-205 sequence and the full length murine DEC-205 sequence, in combination with knowledge available in the art, were sufficient to demonstrate to one of ordinary skill that they had full possession of the complete human DEC-205 protein, and antibody conjugates against the protein, at the time the present application was filed. Indeed, this is shown by the fact that Applicants did, in fact, clone the full length human DEC-205 protein using the very techniques described in the present specification.

A. The Descriptive Text Needed to Satisfy the Written Description Standard Must be Considered in Relation to the Scientific Knowledge in Existence at the time of the Invention, the Skill in the Art, and Correlation of a Disclosed Function to a Known Structure

The mere fact that Applicants' specification does not recite the full length human DEC-205 sequence does not alone mean that the presently claimed methods fail to comply with the written description requirement.

Moreover, Applicants respectfully disagree with the Examiner's assertion that the decision in *Capon v. Eshhar* (418 F.3d 1349, 1357 (Fed. Cir. 2005)) "is not relevant to the

claims under consideration." While the claims may differ from the claims on appeal in *Capon v. Eshhar*, the Court took considerable effort to lay out the underlying framework for determining written description in other cases moving forward, and to clarify that written description, like the enablement requirement, must be determined on a case by case basis. Specifically, the standard for meeting the written description requirement and showing possession of the claimed invention, as articulated by *Capon v. Eshhar*, differs for every patent specification depending upon a number of factors, including **(1) the scientific knowledge in existence at the time of the invention, (2) the skill in the art, (3) the predictability of the claimed subject matter, and (4) correlation of a described function to a known structure**. Again, Applicants do not argue that the claims at issue in *Capon v. Eshhar* were the same as in the present case, rather that the written description standard articulated by the Court, when applied in the present case, is fully satisfied.

Specifically, as discussed further below, the maturity of the science and skill in the art at the filing date of the present invention were such that one of ordinary skill could predictably obtain full-length proteins, such as DEC-205, based on partial sequences, as well as predictably obtain antibodies against the full-length protein (or any region or variants of the protein). As such, Applicants teachings in the specification, combined with the knowledge available in the art, demonstrate that Applicants were in full possession of the presently claimed invention at the time of filing.

B. Isolation and Cloning of Proteins, and Generation of Antibodies Were Highly Mature Technologies at the Time of the Present Invention

At the filing date of the present application (*i.e.*, in 1995), technologies for isolating, characterizing and cloning proteins were highly developed, as were technologies for generating antibodies against such proteins. For example, several well known techniques were available for cloning proteins, including human DEC-205, based on a given partial amino acid sequence of the protein (see, for example, page 20, line 30 through page 21, lines 1-19; as well as page 25, lines 25-31 through page 31, lines 1-16 of the parent application, USSN 09/586,704). Additionally, techniques for expressing cloned proteins (see, for example, page 31, lines 18-31 through page 35, lines 1-30 of the parent application, USSN 09/586,704) and for generating antibodies against the proteins were equally well known (see, for example, page 42, lines 23-31 through page 45, lines 1-19, and particularly page 42, lines 28-31 in the parent application,

USSN 09/586,704). Once armed with a partial amino acid sequence (*i.e.*, a peptide derived from a given protein), it was also well within the skill of the art to use these techniques to generate antibodies against such peptides and to isolate the full-length protein from its natural source.

Applicants specifically illustrated this in relation to mouse DEC-205. In particular, Applicants successfully isolated and characterized full-length mouse DEC-205 from whole murine thymus using mAb NLDC-145, an anti-mouse DEC-205 antibody (see page 63 of the parent application, USSN 09/586,704). Additionally, Applicants successfully raised antibodies against N-terminal peptides from mouse DEC-205 protein (see, for example, page 62, lines 26-32 and page 63, lines 1-15 of the parent application, USSN 09/586,704). This provides evidence that using a partial sequence puts one in possession of a full length sequence, and, thus, could have been applied using the partial human sequence in the present application.

Additionally, in the present application, Applicants teach a partial (C-terminal) sequence (SEQ ID NO.:7) of human DEC-205 protein. Applicants further teach the highly homologous full-length sequence of mouse DEC-205 protein (SEQ ID NO.:10), along with an in-depth characterization of this protein (including its ability to deliver antigen to an active antigen processing compartment of dendritic cells). Applicants also describe well-known techniques for cloning proteins (including human DEC-205) based on a given partial amino acid sequence of the protein, expressing cloned proteins and generating antibodies against such proteins. Based on these teachings, it would have been well within the skill of the art to have isolated the full-length human DEC-205 protein, as well as variants of the human DEC-205 protein, and generate antibodies against this protein.

In fact, as evidenced by the Declaration by Dr. Michel Nussensweig (Appendix A), the cloning techniques and techniques for generating antibodies described in the specification were ultimately successfully used to clone and isolate human DEC-205, and to produce antibodies against full-length human DEC-205. This provides clear evidence that Applicants were in fact indeed in possession of the claimed invention based on the descriptive text provided within the four corners of Applicants' originally filed disclosure.

Rejection of Claims 6-9 and 13-17 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 6-9 and 13-17 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that there is no support in the specification for a human DEC-205 protein comprising an amino

acid sequence as set forth in SEQ ID NO:7. The Examiner further asserts that, although the specification teaches that SEQ ID NO:7 is a peptide derived from DEC-205, there is no support for a DEC-205 protein comprising the peptide wherein the protein could have any amino acids in association with the aforementioned sequences recited in the claim.

As an initial point, it is unclear to Applicants, based on the Examiner's comments, what the distinction is between the 35 U.S.C. § 112, first paragraph, rejection of claims 6-9 and 13-21 discussed immediately above, and the present § 112, first paragraph, rejection of claims 6-9 and 13-17. Indeed, both rejections appear to be based on the same premise, *i.e*, that the claims lack written description because the specification teaches a partial human DEC 205 sequence. Applicants note, however, that the former rejection has been applied to claims 6-9 and 13-21, whereas the present rejection has been applied only to claims 6-9 and 13-17.

Accordingly, with respect to claims 13-17, Applicants again respectfully note that these claims are drawn to methods that employ antibody conjugates defined as binding to a *particular* epitope on human DEC 205, the sequence of which is explicitly taught in the application (SEQ ID NO:7). Therefore, the Examiner's assertion that the specification fails to provide support for a human DEC 205 protein comprising the partial sequence of SEQ ID NO:7 does not provide a basis for rejecting claims 13-17 for lack of written description.

Moreover, for the many reasons discussed above in Section B, Applicants respectfully submit that the specification does indeed provide full support for a human DEC 205 protein comprising SEQ ID NO:7, as recited in claims 6-9. Again, the mere fact that the disclosure teaches partial sequences for human DEC 205 does not alone mean that the claims covering antibody conjugates which bind to human DEC 205 comprising such sequences lack written description. Whether claims 6-9 comply with § 112, first paragraph, depends on a variety of factors, as discussed above in relation to the previous rejection (Section B). When applied in the present case, given the teachings in Applicants' specification, in combination with the skill and knowledge available in the art at the time the present application was filed, clearly demonstrate that Applicants possessed the complete human DEC-205 protein recited in claims 6-9, as well as antibodies that bind to the protein.

As previously discussed in detail, Applicants teach a partial (C-terminal) sequence for human DEC-205 (SEQ ID NO: 7). Based on this partial amino acid sequence, it was well within the skill of the art to have used known techniques to generate antibodies against this peptide, and then to have predictably isolated the full-length protein or variants, from its natural source. In

fact, the maturity of the science and skill in the art at the time of the present invention were such that those of ordinary skill in the art were routinely obtaining full-length proteins based on partial sequences, as well as predictably obtaining antibodies against such full-length proteins. This is specifically attested to in the Declaration submitted by Declaration by Dr. Michel Nussensweig (Appendix A). Further, the fact that Applicants provide an in-depth characterization of mouse DEC-205, including its full-length sequence, which is homologous to human DEC-205, provides further basis for fully meeting the Written Description requirement.

In sum, for at least the foregoing reasons, claims 6-9 and 13-21 fully comply with 35 U.S.C. § 112, first paragraph.

Rejection of Claims 6-9 and 13-17 Under 35 U.S.C. § 112, First Paragraph

Claims 6-9 and 13-17 are newly rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Specifically, the Examiner is of the opinion that the specification fails to disclose how to use the presently claimed methods for the *in vivo* treatment of disease in humans because it "**provides no working examples demonstrating that the instant invention can be used for the induction of tolerance/treatment of disease in vivo in humans or any animal model.**"

Applicants respectfully traverse this rejection for at least the following reasons. First and foremost, as discussed below, working examples are not required to enable a claimed method of treatment. Rather, the disclosure of working examples supporting a claimed invention is only one factor to be considered in determining whether the invention is enabled, and is not solely determinative of the issue.

A. The Existence of Working Examples

In response to the Examiner's suggestion that working examples are required to satisfy the enablement standard, Applicants respectfully note that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether *in vivo* data or working examples are disclosed (M.P.E.P. § 2164.02). In fact, the specification need not contain *in vivo* data or working examples if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)) and, importantly, ***if one of ordinary skill in the art would reasonably accept the supporting disclosure as being enabling***

based on the teachings and/or data that is provided (*In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)). In the present case, this standard is satisfied.

Notwithstanding, contrary to the Examiner's assertion that the present specification ***fails to exemplify "that the instant invention can be used for the induction of tolerance/treatment of disease in vivo,"*** the specification ***does indeed provide multiple in vivo working examples*** (conducted in mouse models), to support the claimed invention. As provided in M.P.E.P. § 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention...***if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.*** As discussed below, mice were routinely used and accepted animal models at the time of filing. Accordingly, the Examiner must accept the present specification as enabling, unless there is evidence to the contrary.

Specifically, Applicants exemplify *in vivo* experiments in mice demonstrating that (1) antigen delivered to dendritic cells *in vivo* induces persistent T cell activation (see page 37, line 14 through page 38, line 7), (2) the absence of persistent T cell activation in mice injected with an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) is not due to a lack of antigen and, therefore, that targeting of antigen to DEC-205 causes persistent T cell activation (see page 38, lines 7-16), and (3) techniques for assessing dendritic cell function in mice receiving multiple doses of an anti-DEC-205 antibody fused to hen egg lysozyme (αDEC/HEL) (see page 38, line 18 through page 39, line 3). In view of these *in vivo* working examples and the fact that mice were (and still are) widely accepted animal models for assessing the clinical value of biological therapeutics, one of ordinary skill in the art would not reasonably doubt that the disclosed mouse data correlates with the claimed invention, nor that the presently claimed methods are fully enabled.

Indeed, as discussed below and evidenced by the references cited by the Examiner, mouse models have long been accepted in the field as being reasonably correlative of human treatment. While clinical studies in humans may ultimately be required to establish human treatments and therapeutic regimens, ***it is readily acknowledged in the art that the basic molecular principle behind a particular method of treatment is often first identified in a murine model.*** In the present case, Applicants were the first to discover that tolerance can be initiated by targeting an antigen to dendritic cells using anti-DEC-205 antibodies, and to prove

this in accepted animal models. The discovery of this molecular principle of tolerance was a typical and pivotal first step in establishing a pervasive concept for disease treatment.

B. Level of Predictability in the Art

The Examiner further asserts that *in vivo* treatment using the presently claimed methods is unpredictable in view of the teachings provided in the prior art. Specifically, the Examiner maintains that it is "unpredictable whether human disease can be treated via enhancing tolerance to a disease antigen" in view of Spack (*Expert Opin Investig Drugs.* 1997 Nov;6(11):1715-27), which teaches that attempts to treat Multiple Sclerosis by inducing tolerance to myelin have been unsuccessful and McKown *et al.* (*Arthritis Rheum.* 1999 Jun;42(6):1204-8), which teach that attempts to treat Rheumatoid Arthritis by inducing tolerance to collagen have been unsuccessful.

Applicants respectfully disagree. Contrary to the Examiner's suggestion, these references cited by the Examiner do not support a lack of predictability for the presently claimed methods (*i.e.*, methods of enhancing the development of tolerance to a preselected antigen). In fact, quite the opposite. Specifically, McKown teach that daily oral treatment with bovine oral type II collagen (CII), when combined with existing therapy in patients with Rheumatoid Arthritis, did not result in a significant clinical improvement in the disease (see pages 1206-1207). However, McKown does not attribute this to a failure to induce tolerance to collagen, as suggested by the Examiner. Instead, the authors state that (1) "[t]he dosage of bovine CII that might induce bystander suppression in RA patients might be much lower than the" dosage used in the present study (see page 1207), (2) that the combination with other therapies, such as prednisone and nonsteroidal anti-inflammatory drugs, "may interfere with the induction of OT [oral tolerance]"(see pages 1207-1208) and (3) that "separate and apart from the drugs that RA patients take are possible agents in the foods of the diverse human diet that might interfere with GALT [gut-associated lymphoid tissue] processing of oral antigen" (see page 1208). Thus, while the combination therapies discussed in McKown were not successful in treating Rheumatoid Arthritis, the authors provide many rationales for this failure, **none of which implicate a failure to induce tolerance to collagen *per se***.

Moreover, importantly, the studies discussed by McKown did **not** involve targeting antigen (*e.g.*, collagen) to DEC-205 and dendritic cells and, as such, do not speak to the predictability of the **presently claimed invention**. Indeed, the presently claimed invention is

based on the discovery that **targeting** of antigen to DEC-205 **enhances** and, therefore, **increases** the predictability of inducing an immune response.

Spack teaches that there was not a statistical significance between Multiple Sclerosis ("MS") patients fed daily capsules of crude bovine myelin versus MS patients fed a placebo in treating their disease. However, the authors also note that those patients who received the myelin capsules "experienced fewer major exacerbations over the 1 year trial period than did patients fed placebo" (see page 1720). Therefore, Spack does, in fact, teach that vaccine treatment had a beneficial effect. Moreover, like McKown, the studies discussed by Spack did **not** involve targeting antigen (*e.g.*, collagen) to DEC-205 and dendritic cells. As such, the teachings of Spack do **not** speak to the predictability of the **presently claimed invention**. Indeed, it is demonstrated in the present application that **targeting** of antigen to DEC-205 **enhances** and, therefore, **increases** the predictability of inducing an immune response.

Additionally, the Examiner asserts that the experimental data from mice provided in the specification is insufficient to enable human treatment *in vivo* in view of (1) Nossal (Fundamentals of Immunology, 2nd Edition, 1989, pages 571-586), (2) Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109), and (3) Mestas *et al.* (*J Immunol.* 2004 Mar 1;172(5):2731-8).

Applicants respectfully disagree that these references cast doubt on the predictability of *in vivo* treatment using the presently claimed methods. In fact, these references highlight the value of using animal models as a preliminary step in establishing a concept for disease treatment in humans.

Specifically, while Nossal note that "[t]here has been a great deal of *discussion* as to whether suppression can be achieved in therapeutic situations by applying the principles coming from model situations (emphasis added)" the authors go on to say that studies involving artificially induced states of tolerance make a "valid contribution" in providing "a balanced overall picture of tolerance" (see pages 571-572). Further, although Tufveson *et al.* (Immunol Rev. 1993 Dec;136:99-109) suggest that data from small animal models should not be the *sole basis* for "clinical decision making"... the authors also state that "it is evident that animal experiments to support modes of clinical action are warranted" (see page 101). Additionally, while Mestas *et al.* point out that mice and humans have obvious differences that "should be taken into account when using mice as preclinical models of human disease," the authors do not discount the value of mouse models and, in fact, state that their goal "is not to suggest that the mouse is an invalid model system for human biology" (see page 2731). Indeed, Mestas *et al.*

teach that "[***m]ice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system***" and that "***mice are the mainstay of in vivo immunological experimentation and in many respects they mirror human biology remarkably well***" (see page 2731).

Moreover, contrary to the Examiner's suggestion that *in vivo* treatment using the presently claimed methods is unpredictable in view of teachings available in the art, Applicants respectfully note that there is ***substantial evidence*** in the art to demonstrate that a molecular principle ***can*** be predictably applied to the development of human therapeutics, once a principle has been identified and tested, for example, in an animal disease model (*e.g.*, an *in vivo* murine disease model). For example, Tysabri, an anti-VLA4 treatment for multiple sclerosis in humans, was presaged by Lawrence Steinman's anti-VLA studies of experimental allergic encephalomyelitis (EAE) in mice; see, for example, Yednock *et al.* (1992) *Nature* 356: 63-66, which concluded that "... therapies designed to interfere with alpha 4 beta 1 integrin may be useful in treating inflammatory diseases of the central nervous system, such as multiple sclerosis." Similarly, Copaxone treatment for multiple sclerosis in humans, was presaged by Ruth Arnon's and Michael Sela's studies with copolymers in EAE in mice and the discovery of synthetic peptides as model antigens; see, for example, Teitelbaum D. *et al.* (1971) *Eur. J. Immunol.* 1: 242-248 which concluded that "[i]n its suppressive activity (the copolymer), it is as effective as the brain encephalitogen itself and thus may be of help both in studies of the mechanism of EASE and as a potential suppressive agent for EAE and other diseases of a similar nature." Additionally, FDA approved IL-2 treatment of cancer in humans was presaged by Steve Rosenberg's studies of mouse melanoma rejection in mice; see, for example, Rosenberg *et al.* (1985) *J. Exp. Med.* 161: 1169-1188, which concluded that "[t]he ready availability of high doses of recombinant human IL-2, and the demonstration of antitumor effects seen in animal models have led us to the initiation of the clinical trials of recombinant IL-2 in humans." Finally, CTLA-4 blockade, for which FDA approval is currently being sought as a new weapon in the treatment of cancer in humans, was presaged by Jim Allison's studies of anti-CTLA treatment of mouse tumors and the discovery of CTLA-4 as a counter-receptor for costimulatory B7 molecules in mice; see, for example, Leach *et al.* (1996) *Science* 271: 1734-1736, which concluded that "[t]hese results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effect immune responses against tumor cells."

These are but a few examples evidencing that a molecular principle ***can*** be predictably applied to the development of human therapeutics. Accordingly, it is clear that *in vivo* mouse models of experimentation are widely accepted as playing a key, initial role in the establishment of methods and therapeutics for treating human disease. As such, it is clear that the working examples set forth in Applicants' specification provide more than sufficient evidence to enable the ordinarily skilled artisan to make and use the claimed invention using only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing remarks, reconsideration and withdrawal of all rejections and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

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Respectfully submitted,

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